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EXAMINER	
GODDARD, LAURA B	

ART UNIT.	PAPER NUMBER
1642	

DATE MAILED: 10/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/816,698	HUNG ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12, 14-16, 18-42* is/are pending in the application.

4a) Of the above claim(s) *24, 27-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14-16,18-26,41 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed August 2, 2006 in response to the Office Action of April 10, 2006, is acknowledged and has been entered. Previously pending claims 12, 14, 15, and 42 have been amended. Claims 13, 17, and 43-75 are cancelled. Claims 12, 14-16, 18-26, 41 and 42 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejection Maintained

Claim Rejections - 35 USC § 112

3. **Claims 12, 14-16, 18-26, 41 and 42 remain rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a WRITTEN DESCRIPTION rejection.

The claims are now drawn to a method of inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject, comprising administering to the subject a mutant Bik polypeptide having an altered amino acid sequence, relative to SEQ ID NO:3, that comprises a substitution at least at a mutation at Thr^{33} and Ser^{35}, wherein the mutant Bik polypeptide induces anti-tumor activity, anti-cell proliferation

activity, and/or pro-apoptotic activity in the subject (claims 12, 19-23, 25, 26), wherein the substitution is a Thr^{33} to Asp^{33} or Ser^{35} to Asp^{35} substitution (claims 14 and 15), wherein the polypeptide further comprises a transduction domain (claims 16), the method of claim 12 further defined as comprising modifying the Bik polypeptide at amino acid position 33, amino acid position 35, or both, wherein the modification results in an inability of the amino acid to be phosphorylated (claim 42).

The specification discloses that a Bik polypeptide comprising anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity, wherein the Bik comprises at least one altered amino acid compared to native Bik is a "mutant Bik" and the alteration of Bik may comprise a modified amino acid or substituted amino acid (p. 7). The specification discloses that mutations, either to similar amino acids or not, may be made anywhere in the Bik polypeptide and that some of these mutants will have the same activity as the exemplary embodiments provided in the specification. For example, threonine, serine, or other appropriate amino acids anywhere within Bik can be substituted. The specification discloses that the mutant Bik polypeptide may further comprise a transduction domain and lists non-limiting examples of a transduction domain such as HIV Tat or penetratin (p. 10). The specification discloses exemplary Bik polypeptides SEQ ID NO:3 and SEQ ID NO:4 (p. 9) and mutant Bik SEQ ID NO:9, which comprises the same sequence as SEQ ID NO:3 except it comprises the Thr^{33} to Asp^{33} and Ser^{35} to Asp^{35} substitutions (p. 9 and 16). The specification does not disclose **any other mutant Bik polypeptides having an altered amino acid sequence** relative to SEQ ID NO:3 that comprises **at least any amino acid mutation** at position 33 and

35, **any mutant Bik having any altered amino acid sequence in addition to** having Thr^{33} to Asp^{33} and Ser^{35} to Asp^{35} substitutions, or **any mutant Bik polypeptide comprising any modification** at position 33 and 35 that results in an inability of the amino acid to be phosphorylated, as broadly encompassed in the claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of **"a mutant Bik polypeptide having an altered amino acid sequence relative to SEQ ID NO:3", "comprises a substitution at least at a mutation at** Thr^{33} and Ser^{35},", **"wherein the substitution is a** Thr^{33} **to** Asp^{33}**", "wherein the substitution is a** Ser^{35} **to** Asp^{35}**", "comprises a transduction domain",** or **"modifying the Bik polypeptide...wherein the modification results in the inability of the amino acid to be phosphorylated".** Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University

of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that " [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. At 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of a mutant Bik polypeptide having an altered amino acid sequence relative to SEQ ID NO:3 that comprises a substitution at least at a mutation at Thr^{33} and Ser^{35}, per Lilly by structurally describing representative mutant Bik polypeptides having an altered amino acid sequence relative to SEQ ID NO:3 or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics,

functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not directly describe a mutant Bik polypeptide having an altered amino acid sequence relative to SEQ ID NO:3 that comprises a substitution at least at a mutation at Thr^{33} and Ser^{35} useful in the claimed invention in a manner that satisfies either the Lilly or Enzo standards. Although the specification discloses mutant Bik polypeptide SEQ ID NO:9, this does not provide a description of the broadly claimed mutant Bik polypeptides having an altered amino acid sequence relative to SEQ ID NO:3 that comprises a substitution at least at a mutation at Thr^{33} and Ser^{35} that would satisfy the standard set out in Enzo because the specification provides no functional characteristics coupled to structural features.

Further, the specification also fails to describe a mutant Bik polypeptide having an altered amino acid sequence relative to SEQ ID NO:3 that comprises a substitution at least at a mutation at Thr^{33} and Ser^{35} by the test set out in Lilly because the specification describes only mutant Bik polypeptide SEQ ID NO:9. Therefore it necessarily fails to describe a representative number of such species.

Thus, the specification does not provide an adequate written description of a mutant Bik polypeptide having an altered amino acid sequence relative to SEQ ID NO:3 that comprises a substitution at least at a mutation at Thr^{33} and Ser^{35} that is required to practice the claimed invention. Since the specification fails to adequately describe the product to which the claimed method of administering to a cell uses, it also fails to adequately describe the method.

Relevant Arguments

4. Applicants state that Examiner notes on pages 4-5 and 8 of the previous Office Action that there is a description of the mutant sequences yet claims 13, 14, and 15 directed to specific substitutions were still rejected under written description. Applicants argue that there is written description of the subject matter of the claims in the specification at least in [0022]. Applicants state that methods of inhibiting proliferation of cancer cells in the specification are disclosed in [0239-0245], [0260-0263], FIGS 1-5 using the specific claimed Bik mutants so one of skill in the art would clearly recognize Applicants had possession of the invention at the time of filing (p. 11-12).

The argument has been considered but is not found persuasive because Applicants are arguing limitations not recited in the claims. The claims are broadly drawn to a mutant Bik **polypeptide** having **any** altered amino acid sequence comprising **any** substitutions at positions Thr^{33} and Ser^{35}. Applicants point to the specification [0239-0245], [0260-0263], and FIGS 1-5, to demonstrate possession of the invention at the time of filing, however, the specific Examples and FIGS referred to in the specification disclose Bik mutant polynucleotide SEQ ID NO:9 and do not describe the broad class of mutant Bik polypeptides having an altered amino acid sequence and any mutations at position Thr^{33} and Ser^{35} that would function as claimed. Applicants refer to paragraph [0022] which contemplates any amino acid substitution at Thr^{33} and Ser^{35} that is not alanine and any modification of a Bik polypeptide that results in failure of the polypeptide to be phosphorylated, and preferably that resultant Bik mutant comprises anti-cell proliferation activity, anti-tumor capability, pro-apoptotic capability or a

combination thereof. Paragraph [0022] does not describe the specific structure of or specific structures associated with the claimed functions of the mutant Bik polypeptide other than SEQ ID NO:9, which comprises the same sequence as SEQ ID NO:3 except it comprises the Thr^{33} to Asp^{33} and Ser^{35} to Asp^{35} substitutions (p. 9 and 16).

New Rejection

(necessitated by amendment)

5. Claims **12, 14-16, 18-26, 41 and 42** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in

determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are now drawn to a method of inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject, comprising administering to the subject a mutant Bik polypeptide having an altered amino acid sequence, relative to SEQ ID NO:3, that comprises a substitution at least at a mutation at Thr^{33} and Ser^{35}, wherein the mutant Bik polypeptide induces anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in the subject (claims 12, 19-23, 25, 26), wherein the substitution is a Thr^{33} to Asp^{33} or Ser^{35} to Asp^{35} substitution (claims 14 and 15), wherein the polypeptide further comprises a transduction domain (claims 16), the method of claim 12 further defined as comprising modifying the Bik polypeptide at amino acid position 33, amino acid position 35, or both, wherein the modification results in an inability of the amino acid to be phosphorylated (claim 42).

The specification discloses a novel therapeutic Bik mutant for cancer. The specification contemplates methods for inhibiting proliferation in a cancer and/or tumor cell comprising contacting the cell with a mutant Bik polypeptide in an amount effective to inhibit cellular proliferation (p. 3, p. 10-11, and Example 12, p. 86). The specification discloses substituting Bik residues Thr^{33} and Ser^{35} with aspartate (Examples 1 to 3, and

6) to produce a mutated Bik nucleic acid for inoculation of the gene into mice with successful results *in vivo* to reduce tumor volume and *in vitro* to induce apoptosis.

One cannot extrapolate the disclosure of the specification to the enablement of the claims because the specification does not provide guidance or working examples for administering a mutant Bik **polypeptide to a subject** that successfully induces anti-tumor activity, pro-apoptotic activity, and/or anti-cell proliferation activity as contemplated and claimed. The specification provides only examples of administering a Bik **polynucleotide** through transfection of cells (p. 75) or lipid delivery to mice (p. 77). Therefore, one of skill in the art would not know how to predictably use a mutant Bik polypeptide having an altered amino acid sequence for *in vivo* anti-tumor activity, anti-cell proliferation activity, or pro-apoptotic activity by administering the polypeptide to a subject.

Mathai et al (J of Biological Chemistry, 2005, 280, 23829-23836) teach that Bik is located at the endoplasmic reticulum from where it elicits pro-apoptotic signals and, given sufficient time, these signals lead to cell death by pathway(s) (p. 23835). Clearly, Bik can only initiate apoptosis if it is inside the cell. Given that Bik requires intracellular initiation of apoptosis, one could not predictably induce apoptosis by administration of a mutant Bik polypeptide to a cell because the polypeptide would be external to the cell and unable to induce apoptosis.

More factors must be considered in addition to internalizing a protein when administering to a cell to induce pro-apoptotic activity, anti-cell proliferation activity, or exert anti-tumor effects. One factor is targeting the protein to a specific tissue or cell

type such as a tumor cell so that surrounding normal tissues are not damaged by the protein's effects. Another factor to consider is the development of an immune response against a mutant polypeptide that is not found naturally occurring in an animal. Administration of an unnaturally occurring protein may induce an immune response against the protein and prevent the protein from reaching its target. Azar et al teach (Apoptosis, 2000, 5:531-542), that the design of specific targeting reagents/drugs still remains the major goal in the treatment of neoplastic diseases and the main aim is to direct therapeutic agents into tumor cells, while avoiding damage to normal tissues and without evoking an immune response (p. 531, col. 1). Azar et al teach the successful targeting of a chimeric Bik protein joined to Gonadotropin releasing hormone (GnRH) that targets adenocarcinomas. Targeting Bik to the cells induced apoptosis *in vitro* in adenocarcinoma cell lines (abstract, p. 533, col. 2; p. 541, col. 2).

Azar et al address the problems of administering their chimeric Bik protein *in vivo*. The reference teaches that the immunogenicity of targeting proteins constitutes a problem to which no practical solution has been found. Azar et al teach that human chimeric proteins that incorporate a human apoptosis-inducing agent, such as Bik, may decrease immunogenicity problems because the apoptosis-inducing agent is of human origin is expected to display reduced immunogenicity in recipients (p. 539, col. 1 and 2; p. 541, col. 2). However, the claims are drawn to a mutant Bik polypeptide that is not the wild-type form and the mutant form may elicit an immune response against the polypeptide, hence, clearing the polypeptide from the animal's body and preventing it from functioning. Given the teaching of Azar et al and Mathai et al, one of skill in the art

could not administer a mutant Bik polypeptide to a subject and predictably induce pro-apoptotic activity, anti-cell proliferation activity, or anti-tumor activity as claimed.

Regarding any substitution at positions Thr^{33} and Ser^{35} or any mutant Bik polypeptide comprising any altered amino acid sequence relative to SEQ ID NO:3 in addition to any substitution at positions Thr^{33} and Ser^{35}, one could not predictably induce pro-apoptotic activity, anti-cell proliferation activity, or anti-tumor activity using a mutant Bik polypeptide with any altered amino acid sequence or any substitutions at positions Thr^{33} and Ser^{35}. Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape of a protein and determines the ability of said protein to fold into unique three-dimensional structures that allows them to function. Bowie et al further teach that certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (p. 1306, cols 1 and 2). Clearly, the three dimensional structure of a protein is critical to its function, particularly relating to the induction of pro-apoptotic activity, anti-cell proliferation activity, or anti-tumor activity. However, neither the specification nor the art of record provide teachings that provide information about the effects any altered amino acid sequence and any amino acid substitution at positions Thr^{33} and Ser^{35} would have on the activity of a mutant Bik polypeptide. This information appears to be critical because the art recognizes (see Bowie et al above) that it is the protein sequence that determines the three dimensional shape of a protein and suggests that the three-dimensional structure of the protein molecule may be essential for the protein's function

and ability to be modulated. Thus, in the absence of guidance in the specification, the effects of the undefined amino acid substitutions, it cannot be predicted and one could not determine how to practice the claimed invention or predict which of the whole universe of broadly claimed mutant Bik polypeptides having any altered amino acid sequence and comprising any substitution at positions Thr^{33} and Ser^{35} would function as claimed with a reasonable expectation of success.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the lack of guidance in the specification, no working examples which would provide guidance to one skilled in the art, the state of the art, the novel nature of the invention, and that no evidence has been provided which would allow one of skill in the art to predict that the claimed invention would function as claimed and contemplated by the specification with a reasonable expectation of success, one of skill in the art would

be forced into undue experimentation to practice the claimed invention.

Relevant Arguments

6. Applicants argue that claim 12 as amended is enabled. Applicants state that Examiner notes a description of the mutant sequences on pages 4-5 and 8 of the previous Office Action. Applicants argue that they disclose methods of inhibiting proliferation of cancer cells in the specification at least at paragraphs [0239]-[0245] and FIGS.1-5 using the specific claimed Bik mutants so one of skill in the art would clearly recognize that Applicants had enabled the claims directed to specific Bik mutants (p. 12).

The argument has been considered but is not found persuasive because Applicants are pointing to *in vitro* examples in the specification for transfecting cultured cancer cells with a mutant Bik **polynucleotide** and an *in vivo* example of inhibiting tumor growth in mice after mutant **Bik gene** delivery by cationic lipid, both of which are outside the scope of the claimed invention. The claims are drawn to a method comprising administering a mutant Bik **polypeptide to a subject** *in vivo.*

7. Applicants argue that given the limited number of amino acids that could possibly be substituted in at either or both of positions 33 and 35, the teaching in the specification to make the substitution, and the disclosure concerning how to test the mutants (for example [0239-0245] and [0256-0259]) it would not be undue experimentation to utilize other Bik mutants (p. 12).

The argument has been considered but is not found persuasive because the claims are not limited to mutations at positions 33 and 35. The claims are broadly drawn to a mutant Bik polypeptide with any altered amino acid sequence relative to SEQ ID NO:3 in addition to any mutations at positions 33 and 35. As stated in the above enablement rejection, the altered amino acid sequences can affect the structure and function of a mutant Bik polypeptide and would not predictably function as claimed. If the mutant Bik polypeptide was limited to any mutations at only positions 33 and/or 35, one of skill in the art could not predict which of the mutants would function as claimed, again, because as stated above, altered amino acid sequences can affect the structure and function of a polypeptide. Further, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention. The specification does not provide guidance or examples for enabling a method of inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject comprising administering a mutant Bik polypeptide having an altered amino acid sequence relative to SEQ ID NO:3 that comprises a substitution at least at a mutation at Thr^{33} or Ser^{35}.

8. All other rejections and objections recited in the Office Action mailed April 10, 2006 are hereby withdrawn.

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. ' 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER